

REVIEW

Use of dihydropyridine calcium channel blockers in the management of hypertension in Eastern Asians: A scientific statement from the Asian Pacific Heart Association

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Dihydropyridine calcium channel blockers (CCBs) are widely prescribed for the management of hypertension in Eastern Asians. In this study, the Asian Pacific Heart Association's Writing Committee reviewed randomized controlled trials that were conducted in the Eastern Asian region and compared a CCB with an antihypertensive drug of another class. These trials studied ambulatory blood pressure, measures of target organ damage and cardiovascular events as outcomes. Eleven trials studied ambulatory blood pressure in hypertensive patients and demonstrated that the 24-h blood pressure reduction with CCBs was greater than with other classes of antihypertensive drugs, with a weighted mean difference of 5 mm Hg systolic and 3 mm Hg diastolic. Twelve trials that studied various measurements of target organ damage in hypertensive patients produced inconsistent results when comparing CCBs and other classes of antihypertensive drugs. Four trials that studied the hard outcomes had limited power, but confirmed the findings of previous placebo-controlled trials in the region and actively controlled trials in Europe and North America; they suggested that CCBs provided superior protection against stroke and that some agents, such as amlodipine, also provided similar protection against myocardial infarction. In conclusion, CCBs should be recommended as a preferred drug for the management of hypertension in the Eastern Asian region to improve blood pressure control and to confront the aggravating epidemic of stroke and coronary heart disease.

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INTRODUCTION

In the Eastern Asian region, dihydropyridine calcium channel blockers (CCBs) are the most widely prescribed drug class for the management of hypertension. According to the 2008 Intercontinental Marketing Services report, ~40% of treated hypertensive patients in this region took a dihydropyridine CCB. The orally administered agents available on the market and their major pharmacokinetic properties are shown in Table 1. CCBs are also the drug class in the Eastern Asian region with the most evidence-based research supporting their efficacy. Several placebo-controlled antihypertensive trials in China have employed a dihydropyridine CCB as the first-line drug for hypertension treatment.^{1–5} Indeed, nitrendipine was used in the Syst-China

(Systolic Hypertension in China trial),^{1,2} nifedipine in the Shanghai trial³ and felodipine in the FEVER (Felodipine Event Reduction) trial.⁴ Despite the fact that these CCBs are short or intermediate acting, active antihypertensive treatment significantly reduced the risk of fatal and non-fatal strokes, the major complication of hypertension in the Chinese population, by 38, 58 and 27% in the Syst-China,¹ Shanghai³ and FEVER trials,⁴ respectively.

In addition to the evidence from these trials, several other factors might also contribute to the use of dihydropyridine CCBs in Eastern Asians. First, CCBs are probably more effective in lowering blood pressure in Eastern Asians, because, when compared with the White population, Eastern Asians have high dietary intakes of sodium⁵ and

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Table 1 Major pharmacokinetic properties of the orally administered dihydropyridine calcium channel blockers

| Calcium channel blocker | t_{max} (h) | Half-life (h) | Vd (l/kg) |
|--|------------------|------------------|--------------|
| Amlodipine | 6–12 | 35–50 | 21 |
| Azelnidipine | 3 | 16 | NR |
| Barnidipine | 1–6 | 10 | NR |
| Benidipine | 0.8–1.1 | 2 | NR |
| Cilnidipine | 1.8–2.2 | 2.5 | NR |
| Efonidipine | 3.6 | 2 | NR |
| Felodipine (extended release) | 2.5–5 | 11–16 | 10 |
| Isradipine | 1.5 | 8–12 | 4 |
| Lacidipine | 5 | 12–15 | NR |
| Lercanidipine | 1.5–3 | 8–10 | NR |
| Manidipine | 1–2 | 5 | NR |
| Nicardipine | 0.5–2 | 1–4 | NR |
| Nifedipine | 0.5 | 2 | 0.6–1.4 |
| Nifedipine (retard, coat-core or controlled release) | 1.6–4 | 7 | NR |
| Nitrendipine | 1.5 | 8 | 13.4 |
| Nisoldipine (extended release) | 1 | 7–12 | 2.7–5.9 |
| Nilvadipine | 1–2 | 15–20 | NR |

Abbreviations: NR, not reported; t_{max} , time to maximal plasma concentration; Vd, volume distribution.

are more likely to be salt sensitive.⁶ Second, CCBs, compared with other classes of antihypertensive drugs, provide more protection against stroke;^{7,8} hence, they are more relevant because the major complication of hypertension in Eastern Asians is stroke rather than myocardial infarction. In the recent Chinese FEVER trial, the incidence of stroke and coronary events was 15.9 and 6.2 per 1000 patient-years, respectively.⁴ Third, dihydropyridine CCBs are particularly useful in the prevention and amelioration of coronary spasm, which is more prevalent in Japanese patients than in Europeans.^{9,10} Indeed, the incidence of coronary spasm after acetylcholine injection was 47 and 15% of arteries, respectively, in 15 Japanese and 19 European patients within 14 days of an acute myocardial infarction ($P < 0.0001$).⁹

The Asian Pacific Heart Association's Writing Committee studied the efficacy of dihydropyridine CCBs in lowering blood pressure and in preventing target organ damage and cardiovascular events. We searched the Chinese, English, Japanese and Korean literature for relevant studies. The electronic search was based on a combination of the keywords 'calcium channel blocker,' 'randomized controlled trial' and at least one of the following: 'ambulatory blood pressure,' 'left ventricular mass,' 'intravascular ultrasound,' 'quantitative coronary angiography,' 'computed tomography angiography,' 'cerebral blood flow,' 'albuminuria,' 'proteinuria,' 'intima-media thickness (IMT),' 'pulse wave velocity (PWV),' 'flow-mediated dilation,' 'microcirculation,' 'stroke' or 'myocardial infarction.' For inclusion in this document, trials must have been conducted in an Eastern Asian country, have a randomized controlled design, have compared a CCB with an antihypertensive drug of another class, and studied the 24-h ambulatory blood pressure and measures of target organ damage or cardiovascular events as outcomes.

EFFICACY IN LOWERING AMBULATORY BLOOD PRESSURE

Numerous studies have been conducted in Eastern Asian countries to compare various antihypertensive regimens. These studies were typically sponsored by the pharmaceutical industry, often had an open design, and were thus vulnerable to observer bias. We therefore

restricted our review to trials that assessed blood pressure by ambulatory blood pressure monitoring. In contrast to mercury sphygmomanometry, this method is less influenced by observer bias and the white coat effect, and provides a large number of blood pressure readings measured during the day and night. In addition, the efficacy of a blood pressure-lowering regimen is dependent not only on the choice of drug or drug class but also on the dosage and combination with other antihypertensive drugs. Thus, the trials included in this part of the review compared monotherapies with a long-acting dihydropyridine CCB and a long-acting antihypertensive drug of another class.

We identified 11 eligible trials, including 6 trials conducted in China^{11–16} and 5 in Japan;^{17–21} 2 had a cross-over design^{17,20} and 9 had a parallel group design.^{11–16,18,19,21} Characteristics of these trials are shown in Table 2. Briefly, 10 trials had an open design and 1 was a double-blind trial. The sample size ranged between 15 and 100. All randomized patients had hypertension, although the definition of hypertension varied. The CCB was amlodipine in 10 trials and nifedipine gastrointestinal therapeutic system (GITS) in 1 trial. These 11 trials included 12 control groups, of which 6, 4, 1 and 1 used angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), a diuretic and a β -blocker, respectively. These study drugs were initiated at the low dose and titrated to the high dose(s) to achieve the goal blood pressure, usually below 140/90 mm Hg. Two trials^{19,21} included a small fraction of patients with additional non-study antihypertensive drugs (<20% in both trials). Nonetheless, these two trials were also included.

The mean or median follow-up time was <6 months in 9 of the 11 trials. These trials showed the superiority of CCBs over the control groups in controlling ambulatory blood pressure, with a difference in 24-h ambulatory systolic blood pressure ranging from 2 mm Hg (see ref. 11) to 11 mm Hg (see ref. 12) (Table 2). Overall, the weighted mean differences in the 24-h systolic/diastolic blood pressure between CCBs and control drugs were 5/3 mm Hg. The difference seemed to occur over the whole day, but was more pronounced with nighttime blood pressure measurements. The difference in nighttime systolic blood pressure ranged from 2 mm Hg (see ref. 11) to 15 mm Hg (see ref. 12). The weighted mean differences in nighttime systolic/diastolic blood pressure were 7/4 mm Hg.

These results were consistent across studies of cross-over vs. parallel group designs, across studies in China and Japan, and across studies of amlodipine or other CCBs as the tested drug and studies of ACE inhibitors or other classes of drugs as the control drug. However, the blood pressure difference was greater in the only blinded trial¹² than in the 10 trials with open designs.

Only 1 trial was truly conducted in a double-blind manner.¹² In this double-blind, double-dummy trial, after a 4-week placebo run-in period, eligible patients (18–80 years of age) with an elevated diastolic blood pressure (95–115 mm Hg) or isolated systolic hypertension (systolic blood pressure >160 mm Hg and diastolic blood pressure <95 mm Hg) were randomly assigned to receive once-daily treatment with amlodipine (5 mg) or enalapril (5 mg) for 14 weeks. Treatment doses were titrated at weeks 4 and 8, if necessary, according to blood pressure response and the patient's ability to tolerate the dose. Patients underwent 24-h ambulatory blood pressure monitoring at the end of the placebo run-in, after the first and last doses of active treatment, and 48 h after the discontinuation of treatment to determine the duration of drug action and to mimic the effect of two missed doses. Thirty-seven patients in each group completed the active treatment phase. After 14 weeks of treatment, amlodipine (mean (s.d.) final dose, 6.3 (2.3) mg) produced greater systolic/diastolic blood pressure

Table 2 Characteristics of trials on 24-h ambulatory blood pressure in hypertensive patients

| Trial | Age, years | | Clinic SBP/DBP, mm Hg | | Antihypertensive treatment, mg | | FU time | Difference in 24-h SBP/DBP, mm Hg ^a |
|---------------------------------------|-----------------|----------------|-----------------------|---------------------|--------------------------------|---------------------------------|-----------------------|--|
| | No. of patients | Entry criteria | Mean (s.d.) | Entry criteria | Control | CCB | | |
| Cross-over studies | | | | | | | | |
| Eguchi <i>et al.</i> ¹⁷ | 46 | ≥60 | 68 (9) | ≥150/90 | 168/92 (26/17) | Temocapril 2-8 | Amlodipine 2.5-10 | 7/2 |
| Ishimitsu <i>et al.</i> ²⁰ | 15 | NR | 52 (11.6) | ≥150/95 | 158/98 (7.9/7.9) | Losartan 25-100 | Amlodipine 2.5-10 | 4/1 |
| Parallel-group studies | | | | | | | | |
| Cao <i>et al.</i> ¹¹ | 75 | 18-65 | NR | ≥140/90-110 | 151.9/96.4 (9.2/7.8) | Fosinopril 10 Indapamide 2.5 | Amlodipine 5 | 5/7 3/3 |
| Eguchi <i>et al.</i> ¹⁸ | 76 | ≥40 | 65.6 (10.6) | 140-180/90-110 | 163.5/92.0 (12.8/12.6) | Valsartan 40-80 | Amlodipine 2.5-5 | 7/2 |
| Ichihara <i>et al.</i> ¹⁹ | 100 | NR | 54.1 (14.0) | ≥140/90 (135/80) | 154.0/96.5 (14.1/7.1) | Valsartan 40-160 | Amlodipine 2.5-10 | 3/-1 |
| Ishimitsu <i>et al.</i> ²¹ | 43 | 37-79 | 56.5 (8.0) | 140-180/90-110 | 163/105 (12/8) | Candesartan 4-12 | Amlodipine 2.5-7.5 | 5/3 |
| Li <i>et al.</i> ¹² | 58 | NR | 55 (12) | ≥140/90 | 152.5/104.5 (8/4) | Perindopril 4-8 | Amlodipine 5-10 | 2/2 |
| Tomlinson <i>et al.</i> ¹³ | 74 | 18-80 | 60.5 (11.6) | /95-114 or >160/<95 | 169.0/94.5 (13.8/9.9) | Enalapril 5-20 | Amlodipine 5-10 | 11/5 |
| Zhang <i>et al.</i> ¹⁴ | 60 | 60-70 | 60.1 (3.6) | ≥140/<90 | NR | Enalapril 10 | Amlodipine 5 | 4/-1 |
| Zhang and Wang ¹⁵ | 76 | NR | 50.2 (9.7) | 160-179/100-109 | 170.2/102.0 (9.7/6.6) | Benazepril 10-20 | Nifedipine GITS 30-60 | 4/0 |
| Zhong <i>et al.</i> ¹⁶ | 60 | 32-65 | 57.5 (8.5) | 140-179/90-109 | 160.0/101.3 (13.5/6.4) | Bisoprolol 5 | Amlodipine 5 | 3/5 |

Abbreviations: CCB, calcium channel blocker; FU, follow-up; GITS, gastrointestinal therapeutic system; NR, not reported; SBP/DBP, systolic/diastolic blood pressure.
^aPositive values indicate larger blood pressure reductions in the CCB group.

reductions than enalapril (mean (s.d.) final dose, 13.3 (6.6) mg) over 24 h (-19.5/-10.4 vs. -8.2/-5.4 mm Hg; $P \leq 0.02$), in the daytime (-19.5/-10.0 vs. -9.9/-6.1 mm Hg; $P < 0.01$) and at night (-20.3/-11.7 vs. -5.6/-3.9 mm Hg; $P < 0.01$). Most of the effect of amlodipine persisted for 72 h after the last dose (24 h, -14.4/-8.2 mm Hg; daytime, -13.8/-8.0 mm Hg; nighttime, -13.6/-7.7 mm Hg), but enalapril had no significant antihypertensive effect at 72 h (24 h, -3.3/-1.8 mm Hg; daytime, -4.3/-2.3 mm Hg; nighttime, -1.9/-1.1 mm Hg).

The results of these trials suggest that Eastern Asians might have a better blood pressure response to CCBs than to other classes of antihypertensive drugs. However, their long duration of action might also have an important part in the more prominent blood pressure reductions by CCBs, particularly amlodipine.

Next, we performed a meta-regression analysis to investigate to what extent the mean blood pressure reduction in each trial was dependent on the mean baseline blood pressure in the CCB and control groups separately. In the CCB groups, both daytime and nighttime systolic blood pressure reduction was significantly ($P \leq 0.05$) and positively associated with blood pressure at baseline, with an enhanced reduction in blood pressure in the trials with a higher mean baseline blood pressure (Figure 1). However, in the control groups, the association was weak and not statistically significant ($P \geq 0.23$) across a large range of blood pressures.

PROTECTION AGAINST TARGET ORGAN DAMAGE

This part of our review focused on randomized controlled trials that investigated the effects of CCBs vs. other classes of antihypertensive drugs on various measures of target organ damage, such as left ventricular hypertrophy, carotid IMT, carotid femoral or brachial-ankle PWV and albuminuria, as proposed by the Chinese²² and Japanese²³ guidelines on the management of hypertension. Trials in patients with congestive heart failure or end-stage renal disease were excluded.

We identified 12 eligible trials, including 9 trials conducted in Japan^{19,21,24-30} and 3 in China.^{15,16,31} The characteristics of these trials are shown in Table 3. Briefly, all trials had an open design. The sample size ranged between 22 and 183. The study subjects had hypertension in all 12 trials; in several trials, study participants had co-morbid conditions such as type 2 diabetes mellitus,^{24,26} coronary artery disease²⁷ and renal impairment.²⁵ Twelve trials included 14 CCB groups and 13 control groups. The CCB was amlodipine in 6 trials, nifedipine GITS, retard, coat-core or controlled release in 5 trials, cilnidipine in 2 trials and efonidipine in 1 trial. The control drug was an ACE inhibitor in 6 trials, an ARB in 6 trials and a β blocker in 1 trial. These study drugs were initiated with the standard dose; in 7 trials^{15,19,21,24,25,27,31} they were titrated to the high dose(s), and in 3 trials^{19,21,27} they were also combined with additional non-study antihypertensive drugs to achieve the goal blood pressure, usually below 140/90 mm Hg of the conventional blood pressure.

Four trials studied brachial-ankle PWV using four different CCBs (amlodipine,^{19,26} nifedipine controlled release^{26,30} or coat-core²⁸ or cilnidipine³⁰) in comparison with an ACE inhibitor (temocapril)³⁰ or ARBs (candesartan²⁶ or valsartan^{19,28,30}). Amlodipine was compared with valsartan in 100 untreated hypertensive patients (50 subjects per group)¹⁹ and with candesartan in 16 hypertensive, diabetic patients (11 vs. 5 subjects).²⁶ In untreated hypertensive patients, after 12 months of follow-up, amlodipine and valsartan decreased brachial-ankle PWV similarly. Furthermore, amlodipine yielded a slightly and non-significantly greater reduction in the 24-h systolic blood pressure (3 mm Hg) and significantly greater reductions in the variability of 24-h and daytime ambulatory systolic blood pressure.¹⁹ However, in a small trial of diabetic and hypertensive patients, after 3 months of

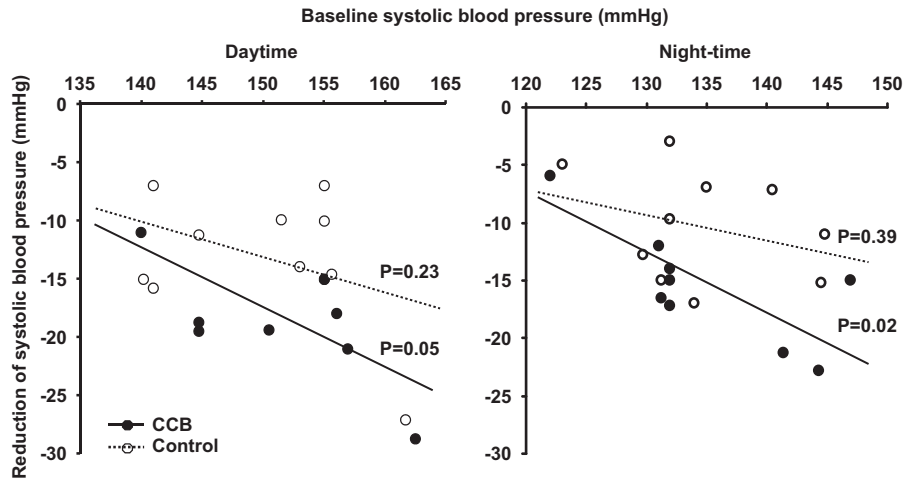


Figure 1 Relation between the mean reduction and baseline level of daytime and nighttime systolic blood pressure by randomization group. The analysis included 10 calcium channel blocker (CCB) groups and 9 control groups from 9 trials,^{11–19} respectively. Two trials were excluded, because daytime and nighttime blood pressures were not reported.^{20,21} The regression line was plotted for the CCB (dot) and control (circle) groups separately, and weighted by the sample size of trials.

follow-up, amlodipine reduced brachial-ankle PWV significantly less than candesartan (157 vs. 637 cm s^{-1} ; $P < 0.01$).²⁶ Nifedipine controlled release^{26,30} or coat-core²⁸ was compared with valsartan in 41 middle-aged (mean age 54 years; 20 vs. 21 subjects)²⁸ and 36 elderly (mean age 72 years; 16 vs. 20 subjects)³⁰ untreated hypertensive patients, with candesartan in 17 (6 vs. 11 subjects) hypertensive and diabetic patients,²⁶ and with temocapril in 36 (16 vs. 20 subjects) elderly, untreated hypertensive patients.³⁰ In all four comparisons, nifedipine reduced brachial-ankle PWV significantly ($P \leq 0.02$) less than valsartan (69 vs. 195 cm s^{-1} and 9 vs. 409 cm s^{-1} in middle-aged and elderly hypertensive patients), candesartan (189 vs. 637 cm s^{-1} in hypertensive and diabetic patients) and temocapril (9 vs. 281 cm s^{-1} in elderly hypertensive patients), despite similar or greater reductions in blood pressure by nifedipine. Cilnidipine ($n=16$) was compared with valsartan ($n=20$) and temocapril ($n=20$) in untreated elderly hypertensive patients.³⁰ Cilnidipine (209 cm s^{-1}) reduced brachial-ankle PWV significantly ($P < 0.01$) less than valsartan (409 cm s^{-1}), but was comparable to temocapril (281 cm s^{-1}).

Three trials studied left ventricular hypertrophy using two different CCBs (amlodipine^{31,21} and cilnidipine²⁹) in comparison with ACE inhibitors (enalapril³¹ or quinapril²⁹) or an ARB (valsartan²¹). After 6 months of treatment with amlodipine, 43 hypertensive patients were randomly assigned to receive candesartan ($n=22$) or to continue amlodipine ($n=21$) for 6 months. After 6 months of the randomized treatment, the left ventricular mass index was significantly reduced by amlodipine (102 to 92 g m^{-2} ; $P < 0.05$), but not by candesartan (103 to 98 g m^{-2}).²¹ However, in 23 previously treated hypertensive patients with left ventricular hypertrophy (left ventricular mass index $\geq 125 \text{ g m}^{-2}$ in men and $\geq 120 \text{ g m}^{-2}$ in women), left ventricular mass index was not influenced by amlodipine after 12 weeks of treatment ($n=13$; 142 to 141 g m^{-2}) but was significantly ($P < 0.05$) reduced by enalapril ($n=10$; 144 to 121 g m^{-2}).³¹ In 60 patients with mild hypertension, after 12 months of treatment, left ventricular mass index was significantly reduced by both cilnidipine ($n=30$; 121 to 106 g m^{-2} ; $P=0.003$) and quinapril ($n=30$; 127 to 116 g m^{-2} ; $P=0.02$). The relative change tended to be greater for patients taking cilnidipine than for those taking quinapril (10.6 vs. 7.6%; $P=0.09$).²⁹

Two trials studied carotid IMT using amlodipine in comparison with ARBs (candesartan,²⁴ losartan,²⁴ telmisartan²⁴ or valsartan^{19,24}).

In an open, randomized study, 104 hypertensive patients with type 2 diabetes were randomly allocated to the amlodipine group ($n=58$) or the ARB group ($n=46$). The ARB group patients received candesartan (4–8 mg per day), losartan (25–50 mg per day), telmisartan (20–40 mg per day) or valsartan (40–80 mg per day). After an average follow-up of 56.9 weeks, amlodipine, compared with ARBs, significantly decreased carotid IMT (–46 vs. +80 μm ; $P < 0.05$). IMT measurement was calculated as the mean of three measurements including one at the site of the greatest thickness and two at sites 1 cm proximal and 1 cm distal to the first site.²⁴ However, in another study of 100 untreated hypertensive patients, after 12 months of follow-up, neither amlodipine ($n=50$) nor valsartan ($n=50$) significantly influenced carotid maximum IMT.¹⁹

Two trials studied proteinuria or albuminuria using two different CCBs (efonidipine²⁵ and amlodipine¹⁹) in comparison with ACE inhibitors²⁵ (enalapril, lisinopril or imidapril) and an ARB (valsartan).¹⁹ In hypertensive patients with renal impairment (serum creatinine, $> 1.5 \text{ mg dl}^{-1}$) or chronic renal parenchymal disease, after 48 weeks of treatment, efonidipine ($n=23$) and ACE inhibitors ($n=20$) produced similar reductions in blood pressure (efonidipine, 161/93–142/82 mm Hg; ACE inhibitors, 163/95–141/83 mm Hg) and did not significantly influence urinary protein excretion ($P > 0.05$). However, in 22 patients with advanced proteinuria ($> 1 \text{ g per day}$), both efonidipine and ACE inhibitors significantly ($P < 0.05$) decreased urinary protein excretion (efonidipine, 2.7 to 2.1 g per day; ACE inhibitor, 3.0 to 2.0 g per day).²⁵ In untreated hypertensive patients, after 12 months of follow-up, valsartan ($n=50$), but not amlodipine, significantly ($P < 0.05$) decreased urinary albumin excretion (valsartan group 40.9 to 18.6 mg g^{-1} of creatinine), despite similar blood pressure reductions.¹⁹

Coronary lumen diameter,²⁷ cerebral blood flow¹⁵ and microcirculation¹⁶ were each studied in one trial. Of the 1665 patients enrolled in the JMIB-B (Japan Multicenter Investigation for Cardiovascular Diseases-B) study, 183 patients participated in the quantitative coronary angiography substudy and had qualified coronary angiograms for analysis. Possible coronary vasodilatation, which may be caused by nifedipine, was excluded by the administration of sufficient isosorbide dinitrate. The minimum luminal diameter of the coronary artery in all measured segments decreased significantly from baseline in the ACE

Table 3 Characteristics of trials on various measures of target organ damage

| Trial | No. of patients | Age, years | | SBP/DBP, mm Hg | | Antihypertensive treatment, mg | | | Outcome measure | FU time | Favorable results |
|---------------------------------------|-----------------|----------------|-------------|-------------------------|------------------------|--------------------------------|-------------------------|-------------------------|-------------------------|------------|-------------------|
| | | Entry criteria | Mean (s.d.) | Entry criteria | Mean (s.d.) | Control | CCB | CCB | | | |
| AAA ²⁴ | 104 | NR | 68.0 (8.1) | NR | 152.3/84.3 (22.0/13.2) | ARBs | Amlodipine 2.5–5 | Amlodipine 2.5–5 | IMT | 56.9 weeks | CCB |
| Chen <i>et al.</i> ³¹ | 60 | NR | NR | ≥ 160/95 | 175.5/99.0 (15.5/6.5) | Enalapril 10–20 | Amlodipine 5–10 | Amlodipine 5–10 | LVM | 12 weeks | Control |
| Hayashi <i>et al.</i> ²⁵ | 43 | NR | 57.5 (14.3) | ≥ 140/90 | 162.0/94.0 (11.9/9.6) | ACE inhibitors | Efonidipine 20–80 | Efonidipine 20–80 | Proteinuria | 48 weeks | Neutral |
| Ichihara <i>et al.</i> ¹⁹ | 100 | NR | 54.1 (14.0) | ≥ 140/90 (135/80) | 154.0/96.5 (14.1/7.1) | Valsartan 40–160 | Amlodipine 2.5–10 | Amlodipine 2.5–10 | BaPWV | 12 months | Neutral |
| | | | | | | | | | IMT | | Neutral |
| Ishii <i>et al.</i> ²⁶ | 22 | NR | 68.2 (7.7) | ≥ 140/90 | 165/90 (18.5/6.0) | Candesartan 8 | Amlodipine 5 | Amlodipine 5 | Albuminuria | 90 days | Control |
| | | | | | | | | | baPWV | | Control |
| Ishimitsu <i>et al.</i> ²¹ | 43 | 37–79 | 56.5 (8.0) | 140–180/90–110 | 163/105 (12/8) | Candesartan 4–12 | Amlodipine 2.5–7.5 | Amlodipine 2.5–7.5 | LVM | 6 months | CCB |
| JMJC-B ²⁷ | 183 | <75 | 64.5 (8.5) | ≥ 150/90–120 or treated | 146/82 (19.5/11.5) | ACE inhibitors | Nifedipine retard 20–40 | Nifedipine retard 20–40 | Coronary lumen diameter | 36 months | CCB |
| Munakata <i>et al.</i> ²⁸ | 41 | 20–70 | 54 (19.2) | > 140/90 | 155/95 (19.2/13.4) | Valsartan 80 | Nifedipine coat-core 20 | Nifedipine coat-core 20 | baPWV | 12 weeks | Control |
| Sakata <i>et al.</i> ²⁹ | 60 | 40–75 | 65 (11) | 140–180/90–105 | 153.5/90 (14/11) | Quinapril 10 | Cilnidipine 10 | Cilnidipine 10 | LVM | 12 months | Neutral |
| Takami and Shigemasa ³⁰ | 76 | ≥ 65 | 71.8 (2.9) | ≥ 160/100 | 186.0/97.7 (20.6/14.3) | Temocapril 2–4 | Nifedipine CR 20 | Nifedipine CR 20 | baPWV | 3 months | Controls |
| | | | | | | Valsartan 80 | Nifedipine CR 20 | Nifedipine CR 20 | | | Controls |
| Zhang and Wang ¹⁵ | 76 | NR | 50.2 (9.7) | 160–179/100–109 | 170.2/102.0 (9.7/6.6) | Benazepril 10–20 | Nifedipine GITS 30–60 | Nifedipine GITS 30–60 | Cerebral blood flow | 4 weeks | CCB |
| Zhong <i>et al.</i> ¹⁶ | 60 | 32–65 | 57.5 (8.5) | 140–179/90–109 | 160.0/101.3 (13.5/6.4) | Bisoprolol 5 | Amlodipine 5 | Amlodipine 5 | Microcirculation | 6 weeks | CCB |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; baPWV, brachial-ankle pulse wave velocity; CCB, calcium channel blocker; CR, controlled release; GITS, gastrointestinal therapeutic system; IMT, intima-media thickness; LVM, left ventricular mass; NR, not reported; SBP/DBP, systolic/diastolic blood pressure. Acronyms of trials are explained in a separate section of this article.

inhibitor group ($n=88$; -0.12 mm; $P<0.001$), but not in the nifedipine retard group ($n=95$; -0.02 mm; $P=0.54$), with a significant difference between the two groups ($P=0.002$).²⁷ In 76 patients with hypertension, nifedipine GITS ($n=38$) was compared with benazepril ($n=38$) in cerebral hemodynamics measured by transcranial Doppler of the middle cerebral arteries. After 4 weeks of treatment, nifedipine GITS, compared with benazepril, significantly increased the blood flow velocity and lowered the blood pulse index.¹⁵ In 60 patients with hypertension, amlodipine ($n=30$) was compared with bisoprolol ($n=30$), and the microcirculation was measured at the left ring fingernail. After 6 weeks of treatment, amlodipine significantly improved microcirculation compared with bisoprolol.¹⁶

More recently, Matsui *et al.*³² compared a CCB (azelnidipine) with a diuretic (hydrochlorothiazide) as an add-on drug to olmesartan monotherapy in 207 hypertensive patients (mean age 68.4 years). After 12 weeks of treatment with olmesartan monotherapy (20 mg per day), patients were randomly assigned to receive 20 mg azelnidipine per day ($n=103$) or 12.5 mg hydrochlorothiazide per day ($n=104$) for 24 weeks. The olmesartan/azelnidipine combination, compared with the olmesartan/hydrochlorothiazide combination, significantly reduced central systolic blood pressure and the aortic PWV, with a between-group difference of 5.2 mm Hg ($P=0.04$) and 0.8 m s⁻¹ ($P<0.001$), respectively. The two combinations had similar influences on the brachial systolic blood pressures with a between-group difference of 2.6 mm Hg ($P=0.29$).

PREVENTION OF CARDIOVASCULAR EVENTS

The dihydropyridine CCBs have been intensively investigated against various classes of antihypertensive drugs in large outcome trials in Europe and North America, including the ACCOMPLISH (Avoiding Cardiovascular Events through COMbination Therapy in Patients Living with Systolic Hypertension),³³ ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),^{34,35} ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)³⁶ and VALUE (Valsartan Antihypertensive Long-term Use Evaluation)³⁷ trials with amlodipine, the STOP-2 (Swedish Trial in Old Patients with hypertension-2) trial with felodipine and isradipine³⁸ and the INSIGHT (International Nifedipine GITS Study—Intervention as a Goal for Hypertension Therapy) trial with nifedipine GITS.³⁹ In the amlodipine trials,^{33–37} amlodipine reduced systolic blood pressure slightly less than chlorthalidone (+1.0 mm Hg)³⁴ and slightly more than lisinopril in ALLHAT (-1.5 mm Hg),³⁵ valsartan in VALUE (-2.0 mm Hg),³⁷ atenolol in ASCOT (-2.8 mm Hg)³⁶ and hydrochlorothiazide in ACCOMPLISH (-0.9 mm Hg).³³ Amlodipine provided similar or increased protection against stroke and myocardial infarction in comparison with chlorthalidone (-7 and -2%),³⁴ lisinopril (-23% ($P=0.003$) and -1%),³⁵ valsartan (-15% ($P=0.08$) and -19% ($P=0.02$)),³⁷ atenolol (-23% ($P=0.0003$) and -13% ($P=0.05$))³⁶ and hydrochlorothiazide (-16 and -22% ($P=0.04$)).³³ In the STOP-2 trial, felodipine or isradipine was compared with the ACE inhibitor and diuretic/ β -blocker groups. Both felodipine and isradipine reduced systolic blood pressure equivalently compared with the other medications and provided slightly superior protection against stroke (-2 and -12% ($P=0.16$)), but inferior protection against myocardial infarction ($+23\%$ ($P=0.02$) and $+18\%$ ($P=0.13$)).³⁸ In the INSIGHT trial, nifedipine GITS, compared with co-amilofide (hydrochlorothiazide 25 mg/amilofide 2.5 mg), reduced systolic blood pressure similarly and provided slightly superior protection against stroke (-13% ; $P=0.60$), but slightly inferior protection against myocardial infarction ($+20\%$; $P=0.19$).³⁹ In summary, in these trials, which were predominantly conducted with Caucasian subjects,

CCBs provided more protection against stroke but had divergent effects on the risk of myocardial infarction, with favorable results in the amlodipine trials.^{7,8}

In Eastern Asians, CCBs were compared with other classes of antihypertensive drugs in four trials on various disease conditions: the CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)⁴⁰ and NICS-EH (National Intervention Cooperative Study in Elderly Hypertensives)⁴¹ trials in hypertensive patients, the JMIC-B trial in patients with hypertension and coronary heart disease⁴² and the JBCMI (Japanese β blockers and Calcium Antagonists Myocardial Infarction) trial in patients within 1 month of acute myocardial infarction.⁴³ All of these trials were conducted in Japan and had an open design (Table 4).

The CASE-J trial compared amlodipine- with candesartan-based antihypertensive regimens in 4728 high-risk hypertensive patients. To achieve the goal blood pressure of 140/90 mmHg or below, diuretics, α blockers, β blockers and/or $\alpha\beta$ blockers could be added. During a mean follow-up of 3.2 years, systolic/diastolic blood pressures were 1.7/0.6 lower in the amlodipine group than in the candesartan group; however, more patients in the candesartan group required the addition of other antihypertensive drugs (54.5 vs. 42.7%; $P < 0.0001$). With relatively small numbers, the incidences of the primary and secondary end points were not statistically different between the two groups. The risk of stroke was slightly but non-significantly lower in the amlodipine group than in the candesartan group (-23%; $P = 0.28$). If the results of the CASE-J trial were combined with those from the VALUE³⁷ and IDNT⁴⁴ trials that also compared amlodipine with an ARB, amlodipine would be shown to provide superior protection against stroke and myocardial infarction by 16 and 17%, respectively.⁸

The NICS-EH (National Intervention Cooperative Study in Elderly Hypertensives) trial included only 414 hypertensive patients, compared two outdated antihypertensive drugs (sustained-release nifedipine vs. trichlormethiazide), had only a total of 39 events during 5 years of follow-up, and was thus inadequately powered.⁴¹

The JMIC-B (Japan Multicenter Investigation for Cardiovascular Diseases-B) trial compared nifedipine retard with ACE inhibitors (enalapril 5–10 mg, imidapril 5–10 mg or lisinopril 10–20 mg, once daily) in 1650 patients with both hypertension and coronary artery disease diagnosed with coronary angiography (stenosis $\geq 75\%$), a history of angina pectoris (> 2 episodes per week) or ST-segment depression of at least 1 mm during the treadmill exercise test.⁴² During a mean follow-up of 36 months, blood pressure reductions were greater in the nifedipine group than in the ACE inhibitor group (-4/-1 mmHg). The incidence of the primary end point (cardiac events: cardiac death or sudden death, myocardial infarction, hospitalization for angina pectoris or heart failure, serious arrhythmia and need for coronary interventions) was similar in the nifedipine (116 events, 14.0%) and ACE inhibitor (106 events, 12.9%) groups (+5%; $P = 0.75$).⁴²

The JBCMI trial compared dihydropyridine CCBs (amlodipine, manidipine, slow-release nifedipine and nisoldipine; $n = 545$) with β blockers (atenolol, bisoprolol, carvedilol and metoprolol; $n = 545$) in 1090 patients within 1 month after acute myocardial infarction.⁴³ At baseline, 52% of patients had a history of hypertension. During a mean follow-up of 455 days, the incidence rates of cardiovascular mortality, recurrent myocardial infarction, refractory angina and non-fatal stroke did not differ between the two groups. However, the incidence of congestive heart failure (4.2 vs. 1.1%; $P = 0.001$) and coronary spasm (1.2 vs. 0.2%; $P = 0.03$) was significantly lower in the CCB group than in the β -blocker group.⁴³

Table 4 Characteristics of outcome trials

| Trial | No. of patients | Disease | Age, years | | SBP/DBP, mm Hg | | Antihypertensive treatment, mg | | | FU time | Difference in SBP/DBP, mm Hg ^a | Favorable results |
|-----------------------|-----------------|----------------|----------------|-------------|---|-------------------------|--------------------------------|-------------------------------------|--|-----------|---|-------------------|
| | | | Entry criteria | Mean (s.d.) | Entry criteria | Mean (s.d.) at baseline | Control | CCB | | | | |
| CASE-J ⁴⁰ | 4728 | HT | | 63.8 (10.5) | $\geq 140/90$ (<70 years) or $\geq 160/90$ (≥ 70 years) | 162.8/91.7 (14.2/11.2) | Candesartan 4–8 | Amlodipine 2.5–10 | | 3.2 years | 1.7/0.6 | Neutral |
| JBCMI ⁴³ | 1090 | AMI (<1 month) | NR | 64.4 (11.5) | NR | NR | β blockers | CCBs | | 455 D | NR | CCB |
| JMIC-B ⁴² | 1650 | HT & CAD | <75 | 64.5 (8.5) | $\geq 150/90$ –120 or treated | 146/82 (19.5/11.5) | ACE inhibitors | Nifedipine retard 20–40 | | 36 months | 4/1 | Neutral |
| NICS-EH ⁴¹ | 414 | HT | ≥ 60 | 69.8 (6.5) | 160–220/<115 | 172.3/93.8 (11.9/10.2) | Trichlormethiazide 2–4 | Nicardipine sustained release 40–80 | | 3 years | 0/-2 | Neutral |

Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; CAD, coronary artery disease; CCB, calcium channel blocker; FU, follow-up; HT, hypertension; NR, not reported; SBP/DBP, systolic/diastolic blood pressure. Acronyms of trials are explained in a separate section of this article.

^aPositive values indicate larger blood pressure reductions in the CCB group.

PERSPECTIVES AND CONCLUSIONS

In Eastern Asians, monotherapy with the recommended dosages of the dihydropyridine CCBs, mainly amlodipine, is more efficacious in lowering blood pressure when compared with other classes of antihypertensive drugs. The difference in the 24-h systolic/diastolic blood pressure measurements between the groups could be as large as 5/3 mm Hg. This superiority, among others, can be a driving factor for the wide and even wider use of CCBs in the Asian region.

With regard to target organ protection with CCBs, the evidence in Eastern Asians is rather weak. The results of these trials were sometimes contradictory, probably because of chance findings in small studies, and might be dependent on the choice of agents or the measures of target organ damage. Moreover, it is noteworthy that the improvement in these intermediate measures of target organ damage cannot necessarily be translated into prevention of stroke and myocardial infarction, although these measures might be predictive of cardiovascular events in observational studies. Nonetheless, these studies could generate valuable hypotheses to be tested in outcome trials.

The actively controlled trials in Eastern Asians, although few and small, provided evidence on the use of CCBs in the prevention of cardiovascular events. These studies confirmed the findings of previous placebo-controlled trials in the Eastern Asian region and were consistent with the results of large outcomes trials in Europe and North America. CCBs might provide superior protection against stroke and coronary spasm. These advantages of CCBs might be particularly relevant for cardiovascular prevention in the Eastern Asian region, where stroke is the major complication of hypertension and coronary spasm is prevalent and probably one of the major causes of myocardial infarction.⁴⁵ In addition, specific agents such as amlodipine might also provide similar or even superior protection against myocardial infarction.

According to the current evidence in trials on blood pressure control, target organ protection and cardiovascular prevention in Eastern Asians, CCBs should probably be recommended as the preferred drug in the management of hypertension in the Eastern Asian region to improve blood pressure control and to confront the aggravating epidemic of stroke and coronary artery disease. National guidelines in the region, and possibly regional guidelines in the future, should provide clearer recommendations on the choice of antihypertensive drugs and recommend the use of CCBs as the initial therapy in patients with uncomplicated hypertension.

ACRONYMS

AAA (Amlodipine *vs.* ARB in Atherosclerosis study);²⁴ ACCOMPLISH (Avoiding Cardiovascular Events through COMBination Therapy in Patients Living with Systolic Hypertension);³³ Anglo-Scandinavian Cardiac Outcomes Trial;³⁶ CASE-J (Candesartan Anti-hypertensive Survival Evaluation in Japan Trial);⁴⁴ FEVER (Felodipine Event Reduction Study);⁴ JBCMI (Japanese β blockers and Calcium Antagonists Myocardial Infarction);⁴³ JMIC-B (Japan Multicenter Investigation for Cardiovascular Diseases-B);⁴² ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial);^{34,35} INSIGHT (International Nifedipine GITS Study—Intervention as a Goal for Hypertension Therapy);³⁹ NICS-EH (National Intervention Cooperative Study in Elderly Hypertensives);⁴¹ STOP2 (Swedish Trial in Old Patients with hypertension-2);³⁸ Syst-China (Systolic Hypertension in China trial);^{1,2} VALUE (Valsartan Antihypertensive Long-term Use Evaluation).³⁷

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